Effects of Second and Subsequent Lines of Chemotherapy for Metastatic Breast Cancer☆

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Abstract

Continuing cytotoxic chemotherapy is justified in metastatic breast cancer. However, the clinical effects of successive treatment have not been evaluated. In the present study, we assessed 240 patients with metastatic breast cancer who received multiple lines of cytotoxic chemotherapy regimens. We confirmed that the beneficial effects of subsequent chemotherapy for patients with a durable response from previous treatment.

Background: We assessed the effect of chemotherapy regimens beyond first-line agents on the clinical outcomes in patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC). **Patients and Methods:** We included 240 patients who were prospectively enrolled into various clinical trials and were receiving cytotoxic chemotherapy for HER2-negative MBC at the National Cancer Center, Korea, from October 2002 to September 2012. Clinicopathologic data were collected for the analysis. **Results:** A total of 240, 209, and 166 patients received first-, second-, and third-line chemotherapy, respectively. The median age was 49 years (range, 28-77 years), and most had hormone receptor-positive cancer (n = 177; 73.8%). The median progression-free survival (PFS) was 7.6 months for first-line (PFS1) versus 5.1 months for second-line (PFS2) versus 3.6 months for third-line (PFS3) chemotherapy. The PFS from previous chemotherapy significantly affected subsequent PFS: PFS1 for PFS2, PFS1 $\geq$ 7.6 months, hazard ratio (HR) 0.647; 95% confidence interval (CI), 0.0.484-0.864 ($P = .003$); PFS2 for PFS3, PFS2 $\geq$ 5.1 months, HR 0.676; 95% CI, 0.0.484-0.944; $P = .022$). The median overall survival was 31.2 months (95% CI, 26.4-36.0 months). Hormone receptor positivity (HR 0.548; 95% CI, 0.261-0.499; $P < .001$) and PFS1 $\geq$ 7.6 months (HR 0.361; 95% CI, 0.393-0.765; $P < .001$) were significant factors for survival on multivariate analysis. **Conclusion:** The efficacy of previous treatment significantly affected the outcomes of subsequent treatment. We have confirmed that the succession of chemotherapy is justified in patients with MBC who benefited from previous chemotherapy.

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Keywords: Chemotherapy, Drug resistance, Metastatic breast cancer, Progression free survival, Response rate

Introduction

The incidence and prevalence of breast cancer are increasing globally. Although a greater proportion of women are diagnosed in early disease stages because of national screening programs and increasing awareness, 3% to 5% of patients still present with metastatic disease at diagnosis.[1,2] In addition, 20% to 85% of patients who undergo complete resection develop distant metastases.[3] Metastatic breast cancer (MBC) is typically incurable, and one of the important aims of treatment is symptom palliation. The median survival of patients with MBC is 18 to 24 months.[4] As understanding about cancer has broadened, several targeted therapies have proved effective against MBC that has shown resistance to previous chemotherapy regimens such as trastuzumab emtansine,[5] lapatinib,[6] and everolimus.[7]

Although randomized trials of some first-line regimens have shown improved survival and quality of life (QoL), few studies have explored the effects of chemotherapy beyond first-line agents. Excluding hormonal therapy, anthracycline- and taxane-containing regimens are considered the first-line chemotherapy agents for HER2$^-$ MBC.[8,9] After tumors progress on these first-line regimens, other chemotherapeutic agents can be used, including capecitabine, gemcitabine, vinorelbine, and cisplatin. Although these drugs have been evaluated as second- or third-line treatment,[10-12] survival gain and preservation of QoL remain debatable. Therefore, a systematic investigation of the benefit of chemotherapy beyond first-line treatment has become necessary, with the introduction of these more effective chemotherapeutic drugs for the treatment of MBC.

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In the present study, we assessed the effect of multiple chemotherapy regimens, specifically beyond the first line, on the survival of patients with HER2$^-$ MBC.

Patients and Methods

Study Population and Treatment

We included 240 patients who had received cytotoxic chemotherapy for MBC at the National Cancer Center, Korea, from October 2002 to December 2012. All the patients had been prospectively enrolled in various phase II and III clinical trials for MBC. A total of 240, 209, and 166 patients received first-, second-, and third-line chemotherapy, respectively. The administered chemotherapeutic regimens are listed in Supplemental Table 1 (available in the online version). A total of 48 patients (20%) participated in > 2 clinical protocols subsequently after 1 regimen had failed. Most patients had received chemotherapy until the documentation of disease progression, unacceptable toxicity, or patient and clinician decision.

Clinical data, such as performance status, age, and the presence of visceral involvement, were collected at the initiation of the first-line chemotherapy for MBC. In addition, data on hormone receptor and HER2 status, Ki-67 expression, and types of adjuvant systemic treatment were collected for all patients from their medical records. Patients with an initial diagnosis of metastatic disease were classified as having de novo stage IV disease. In the present study, we defined hormone receptor–positive disease as > 10% of tumor cells with estrogen receptor or progesterone receptor expression on immunohistochemical analysis.

Statistical Analysis

Five groups of chemotherapy were defined according to the principle agents used: anthracyclines, taxanes, capecitabine, gemcitabine or vinorelbine, and other drugs. The patients who received combination regimens such as a taxane plus capecitabine or a taxane plus anthracycline were arbitrarily assigned to the taxane group. The Response Evaluation Criteria in Solid Tumors, version 1.0, was used to assess the efficacy for measurable or evaluable lesions using the clinical or radiologic findings. The progression-free survival (PFS) of patients receiving each drug was defined as the interval from the date of the first administration of the specific drugs to the date of the first documented tumor progression or death from any cause. Overall survival (OS) was defined as the interval from the date of the first administration of the specific drugs to death from any cause or the last follow-up date. PFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to control for various clinical factors and to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for each factor. Proportions were compared using 2-way tables and χ^2 tests. All *P* values were 2 tailed, with 5% significance levels. All statistical analyses were performed using STATA, version 10.0.

Results

Patient Characteristics and Treatment Efficacies

A total of 240 patients, with a median age of 49 years (range, 28-77 years) were analyzed. Most patients had hormone receptor–positive MBC (n = 177, 73.8%), and 57 patients (23.8%) were initially diagnosed as having de novo stage IV disease. The median distant disease-free interval was 25.4 months (range, 0-246.4 months), and 150 patients (62.5%) had visceral metastasis at diagnosis (Table 1). Of the 240 patients, 122 (50.8%) received anthracycline-based and/or taxane-based adjuvant chemotherapy, and 89 (50.3%) of those with hormone receptor–positive tumors received palliative antihormonal therapy for metastatic disease.

The efficacy stratified by the lines of chemotherapy in terms of response and PFS is presented in Table 2. The most frequently delivered chemotherapeutic regimens differed by the line of chemotherapy. A total of 168 patients (70.0%) received taxane-based chemotherapy as first-line therapy; 85 (40.7%) received capecitabine-containing regimens as second-line therapy; and 90 (54.2%) received gemcitabine- or vinorelbine-containing regimens as third-line chemotherapy. The median PFS decreased with the advancing lines of chemotherapy: 7.6 months for first line (mPFS1) versus 5.1 months for second line (mPFS2) versus 3.6 months for third line (mPFS3). Although the objective response rates to chemotherapy decreased with the increasing number of lines (Table 2), the differences in the rates were statistically significant in the same lines, depending on the chemotherapeutic regimen. As first-line therapy, anthracycline-based chemotherapy

Table 1 Patient Characteristics (n = 240)

Characteristic	Median (Range) or Patients (%)
Age (years)	49 (28-77)
DFI (mo)	25.4 (0-246.4)
Patients with DFI	
<2 years	118 (47.2)
≥2 years	132 (52.8)
De novo stage IV	57 (23.8)
ER/PgR$^+$/HER2$^-$	177 (73.8)
ER/PgR2/HER2$^-$	63 (26.3)
PS	
0-1	199 (82.9)
2	19 (7.9)
Missing	22 (9.2)
Adjuvant chemotherapy	
No	71 (29.6)
CMF	46 (19.2)
AC or FAC/FEC	54 (22.5)
AC-T	68 (28.3)
Other	1 (0.4)
Previous hormonal therapy	
Adjuvant	165 (68.7)
Palliative	77 (32.1)
Visceral involvement	
Yes	150 (62.5)
No	90 (37.5)

Abbreviations: AC = doxorubicin, cyclophosphamide; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; DFI = disease-free interval; ER = estrogen receptor; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; HER2 = human epidermal growth factor receptor 2; PgR = progesterone receptor; PS = performance status; T = docetaxel or paclitaxel.

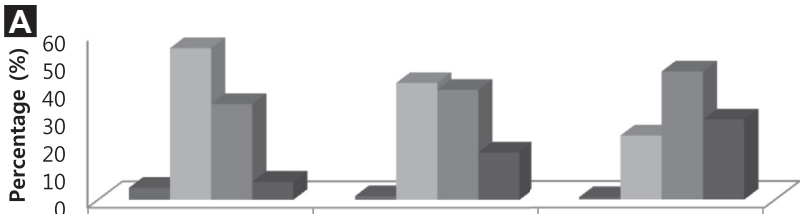
Table 2 Clinical Efficacy of Chemotherapeutic Regimens in Each Line of Therapy

Regimen	First Line (n = 240) (mPFS1 7.6 mo; 95% CI 6.7-8.5)		Second Line (n = 209) (mPFS2 5.1 mo; 95% CI 4.3-5.9)		Third Line (n = 166) (mPFS3 3.6 mo; 95% CI 2.8-4.4)	
	PFS1 (mo)	ORR1 (%)	PFS2 (mo)	ORR2 (%)	PFS3 (mo)	ORR3 (%)
Anthracycline based	8.6 (4.9-12.3)	26 (60.5)	5.2 (4.4-6.0)	18 (39.1)	3.1 (2.8-3.4)	1 (11.1)
Taxane based	7.7 (6.8-8.6)	91 (54.8)	6.3 (3.3-9.3)	24 (51.1)	2.4 (1.0-3.8)	1 (16.7)
Capecitabine based	5.7 (2.3-9.1)	10 (35.7)	5.8 (3.4-8.2)	33 (38.8)	5.5 (3.6-7.4)	20 (35.7)
Gemcitabine/ vinorelbine based	NA	NA	4.0 (2.8-5.2)	6 (19.4)	3.0 (2.0-4.0)	11 (11.4)
P value	.788	.105	.015	.048	.072	.196

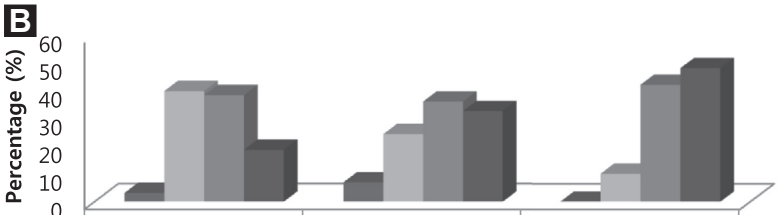
Data in parentheses are 95% CIs, unless otherwise noted.
Abbreviations: CI = confidence interval; mPFS1 = median progression-free survival of first-line therapy; mPFS2 = median progression-free survival of second-line therapy; mPFS3 = median progression-free survival of third-line therapy; NA = not available; ORR = objective response rate (complete response plus partial response).

showed the highest response rate (60.5%). For second-line therapy, a taxane-based regimen yielded the highest response rate (51.1%). Finally, for third-line therapy, capecitabine-based chemotherapy resulted in a 35.7% response rate. The responses to chemotherapy also differed by hormone receptor positivity (Figure 1). Moreover, the rate of primary resistance was much greater in hormone receptor−negative cases (18.5% vs. 6.5%), and resistance to chemotherapy emerged rapidly in this latter population, which led to a lack of benefit from subsequent therapy (Figure 1B).

Figure 1 Effect of the Response of Chemotherapy According to the Line of Therapy. (A) Hormone Receptor (HR)−Positive Breast Cancer. (B) HR^{-} Breast Cancer Population



	First line (N=177)	Second line (N=151)	Third line (N=116)
CR	4.3	1.3	0.8
PR	54.7	42.1	23.1
SD	34.5	39.6	46.3
PD	6.5	17	28.9



	First line (N=63)	Second line (N=58)	Third line (N=50)
CR	3.1	6.9	0
PR	40	24.1	10
SD	38.5	36.2	42
PD	18.5	32.8	48

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Analysis of Factors Potentially Predictive of Survival From Chemotherapy

On univariate analysis, hormone receptor positivity (HR 0.53; 95% CI, 0.43-0.78; $P < .001$), de novo stage IV disease (HR 0.64; 95% CI, 0.47-0.87; $P = .005$), and the use of adjuvant chemotherapy (HR 1.19; 95% CI, 1.07-1.33; $P = .002$) were significantly associated with the mPFS1 (Table 3). Of these factors, hormone receptor positivity (HR 0.57; 95% CI, 0.42-0.76; $P < .001$) remained as a significant predictive factor for longer PFS1 on multivariate analysis.

To investigate the effects of immediate previous drugs on subsequent regimens, the patients were categorized according to the mPFS duration for each line: those with a short duration of disease control (less than the mPFS of each line) and those with prolonged disease control (mPFS or longer for each line). In patients receiving second-line therapy, a PFS1 > 7.6 months (HR 0.62; [95% CI, 0.47-0.83; $P = .001$) was an important factor for longer PFS2, along with hormone receptor positivity (Table 3). Similarly, PFS2 for > 5.1 months was a significant factor for longer PFS3 in patients receiving third-line therapy (HR 0.62; 95% CI, 0.44-0.85; $P = .003$).

The median OS was 2.6 years (95% CI, 2.2-3.0 years) and was significantly affected by hormone receptor status (positive vs. negative, 3.4 years [95% CI, 3.0-3.8 years] vs. 1.7 years [95% CI, 1.3-2.1 years]). The response rates and PFS after first-line therapy were significantly associated with OS. Figure 2 shows the survival difference according to the response and mPFS1 in both in hormone receptor−positive and hormone receptor−negative breast cancer. The factors for prolonged survival after the first enrollment were hormone receptor−positive disease (HR 0.57; 95% CI, 0.41-0.77; $P = .001$), PFS1 longer than the median (7.6 months) (HR 0.41; 95% CI, 0.29-0.56; $P < .001$), and an objective response to first-line therapy (HR 0.56; 95% CI, 0.41-0.77; $P < .001$; Table 4).

Discussion

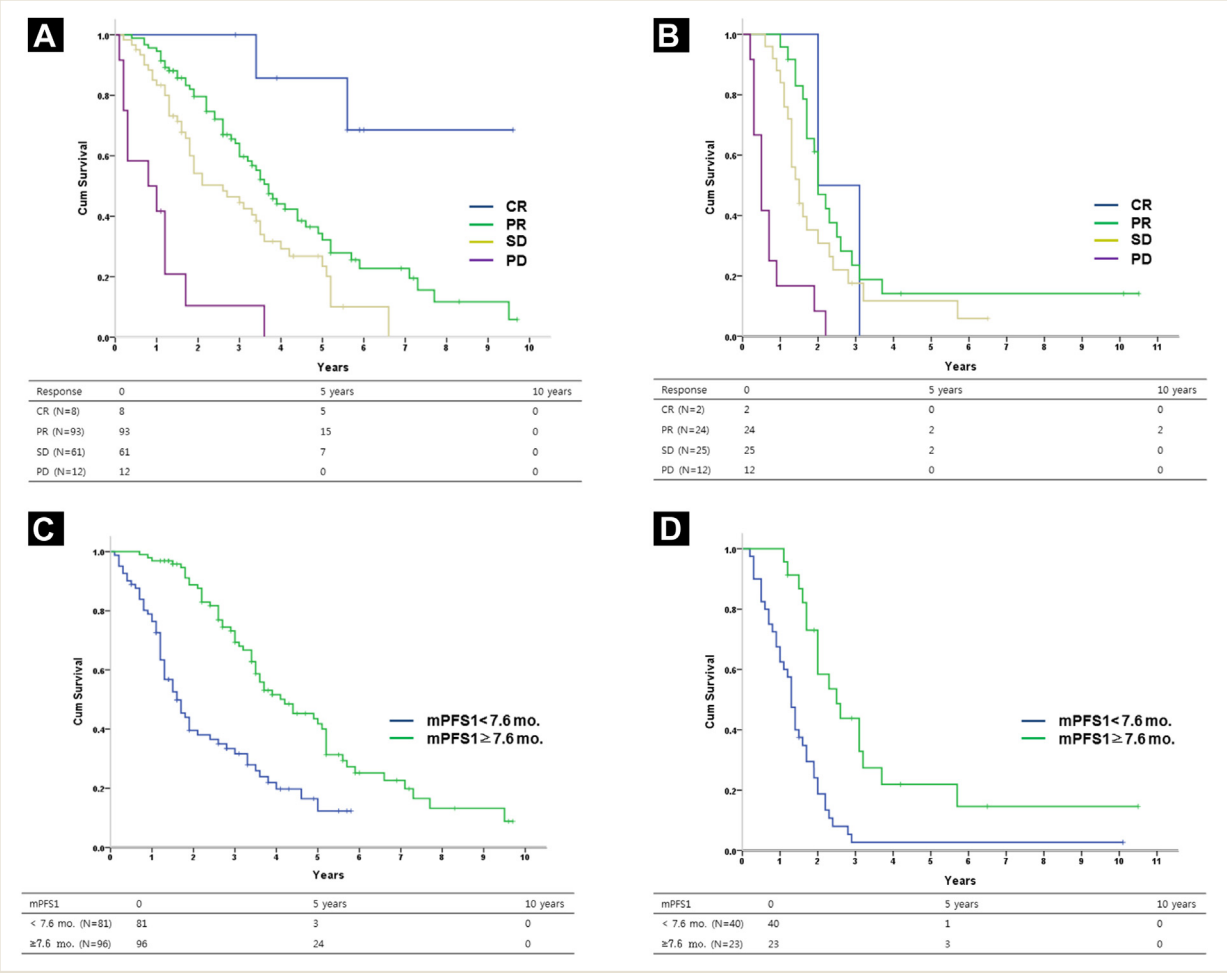
Although MBC can only rarely be cured, it can be managed with effective treatment strategies. The therapeutic goals in this setting are prolongation of survival and symptom control resulting in good QoL. One population-based study revealed that new therapeutic agents, including taxane, aromatase inhibitors, and anti-HER2 therapy for MBC, have been associated with improved survival.[13] However, the aims of treatment can differ according to multiple factors because MBC is a heterogeneous disease. These factors include the specific tumor biology, the disease progression rate, the presence of visceral metastases, a history of previous therapy and the response, the toxicity of the therapeutic agents, and patient preference. In the present study, we assessed the clinical effects of subsequent chemotherapy after first-line therapy. We sought to identify the factors associated with the benefits and justification of prolonged chemotherapy regimens. The clinical benefit of chemotherapy according to the PFS correlated

Table 3 Analysis for PFS in Each Line of Chemotherapy

	Univariate Analysis		Multivariate Analysis	
Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
PFS1				
De novo stage IV disease (yes vs. no)	0.64 (0.47-0.87)	.005	0.74 (0.48-1.15)	.177
Visceral disease (yes vs. no)	1.14 (0.87-1.50)	.335		
DFI (>2 years vs. ≤2 years)	1.00 (0.77-1.30)	.976		
Hormone receptor (+ vs. −)	0.53 (0.43-0.78)	<.001	0.55 (0.41-0.75)	<.001
Age (≤45 years vs. >45 years)	1.05 (0.80-1.37)	.748		
Adjuvant chemotherapy (yes vs. no)	1.19 (1.07-1.33)	.002	1.11 (0.95-1.30)	.198
PFS2				
De novo stage IV disease (yes vs. no)	0.79 (0.57-1.11)	.171		
Visceral disease (yes vs. no)	1.05 (0.78-1.40)	.764		
DFI (>2 years vs. ≤2 years)	0.81 (0.61-1.08)	.147		
Hormone receptor (+ vs. −)	0.58 (0.42-0.80)	.001	0.60 (0.44-0.82)	.001
Age (≤45 years vs. >45 years)	1.07 (0.80-1.44)	.641		
Adjuvant chemotherapy (yes vs. no)	1.15 (1.02-1.29)	.022	1.11 (0.99-1.25)	.078
Median PFS1 ≥7.6 mo	0.62 (0.47-0.83)	.001	0.65 (0.48-0.86)	.003
PFS3				
De novo stage IV disease (yes vs. no)				
DFI (>2 years vs. ≤2 years)	0.70 (0.50-0.96)	.027	0.74 (0.53-1.05)	.087
Hormone receptor (+ vs. −)	0.44 (0.31-0.64)	<.001	0.51 (0.35-0.73)	<.001
Adjuvant chemotherapy (yes vs. no)	1.17 (1.02-1.34)	.023	1.18 (1.03-1.35)	.019
Median PFS2 ≥5.1 mo	0.62 (0.44-0.85)	.003	0.68 (0.48-0.94)	.022

Abbreviations: CI = confidential interval; DFI = disease-free interval; HR = hazard ratio; mPFS1 = median progression-free survival of first-line therapy; mPFS2 = median progression-free survival of second-line therapy; mPFS3 = median progression-free survival of third-line therapy; PFS = progression-free survival.

Figure 2 Overall Survival According to Response and Median Progression-Free Survival (mPFS) of First-Line Therapy in Both Hormone Receptor (HR)—Positive and HR$^-$ Breast Cancer. (A) HR$^+$ ($P < .001$). (B) HR$^-$ ($P < .001$). (C) HR$^+$ ($P < .001$). (D) HR$^-$ ($P < .001$)



Abbreviations: Cum = cumulative; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Table 4 Analysis for Clinical Factors Associated With Overall Survival in All Patients

	Univariate Analysis		Multivariate Analysis	
Factor	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
mPFS1 (≥7.6 mo vs. <7.6 mo)	0.34 (0.25-0.46)	<.001	0.41 (0.29-0.56)	<.001
OR in first therapy (yes vs. no)	0.43 (0.32-0.59)	<.001	0.56 (0.41-0.77)	<.001
DFI (>2 years vs. ≤2 years)	0.77 (0.57-1.04)	.093	—	—
Hormone receptor (+ vs. −)	0.48 (0.35-0.67)	<.001	0.57 (0.41-0.80)	.001
Age (≤45 years vs. >45 years)	1.16 (0.85-1.59)	.345	—	—
Visceral disease (yes vs. no)	0.99 (0.73-1.35)	.969	—	—
Adjuvant chemotherapy (yes vs. no)	1.23 (1.08-1.39)	.001	1.60 (0.98-1.37)	.079
De novo stage IV disease (yes vs. no)	0.35 (0.45-0.93)	.018	1.07 (0.66-1.71)	.793

Abbreviations: CI = confidence interval; DFI = disease-free interval; HR = hazard ratio; mPFS1 = median progression-free survival of first-line therapy; OR = objective response (complete response plus partial response); PFS = progression-free survival.

significantly with the objective response rate, regardless of hormone receptor status. Routinely, both anthracycline- and taxane-based chemotherapy regimens have been recommended as the initial therapy for MBC.[8,14] In the present series, > 80% of patients received anthracycline or a taxane as their first-line chemotherapy. Subsequently, capecitabine was used for the second- or third-line therapy (see Supplemental Table 1 in the online version). According to our data, the PFS with anthracycline- or taxane-based chemotherapy was longer than that with capecitabine-based therapy in the same line. All the patients who received capecitabine as first-line therapy had already been exposed to anthracycline and/or taxane in an adjuvant or a neoadjuvant setting and could have acquired resistance to multiple drugs. Similarly, we could assume that patients with de novo stage IV disease showed a significantly prolonged PFS after first-line treatment compared with those who had received adjuvant or neoadjuvant chemotherapy (Table 3).

In general, hormone receptor−positive disease has been regarded as being less sensitive to cytotoxic chemotherapy than hormone receptor−negative disease, which has been clearly demonstrated by a lower pathologic complete response rate in the neoadjuvant setting.[15-17] However, we found that the PFS was significantly longer in those patients with hormone receptor−positive disease for every line of treatment in the metastatic setting. These findings were related to the greater disease control rate in the hormone receptor−positive tumors than in the hormone receptor−negative tumors (Figure 1). It is relevant that previous results for hormone receptor−negative tumors showed a poor prognosis because of rapid acquisition of drug resistance despite the initial responses.[18-21]

From our data, around 5% to 17% of patients developed primary resistance to first-line cytotoxic chemotherapy, and the proportion of chemotherapy resistance increased by two- to threefold for the subsequent line of therapy, regardless of hormone receptor positivity. Furthermore, the patients who had had no response to previous therapy showed a strong tendency for subsequent treatments to fail. The phenomenon became more prominent with more advanced lines of treatment (Figure 1). Therefore, the response to previous treatment should be considered when making clinical decisions to use more than third-line therapy.

Our cohort data showed that the PFS of first-line therapy was strongly associated with OS, consistent with previous results.[22-24] In addition, the response to the first-line therapy and the presence of hormone receptors were important prognostic factors for survival. This information will be helpful for assessing the prognosis and as a guideline in the treatment of patients with MBC. Every effort to overcome resistance will be necessary for the patients who specifically have primary resistance, including enrollment into clinical trials with new targeted drugs.

The present study had several limitations. It was a retrospective study that included patients who had been enrolled in various clinical trials. Therefore, the chemotherapeutic regimens were diverse, although all these regimens could be grouped by anthracycline-, taxane-, or capecitabine-based combinations. In addition, the present study did not assess the toxicity and QoL issues of the treatment regimens. QoL is an important issue in the metastatic setting, just as much as the treatment response and survival. For these issues, prospective cohort studies are needed.

Conclusion

Successive chemotherapy is necessary for patients with MBC and has been demonstrated to prolong OS and increase the QoL. However, these effects from chemotherapy decreased with more advanced lines of treatment. Patients with no response to a previous line of therapy showed a strong tendency for subsequent treatment to fail. Our results have shown that the PFS of first-line therapy, the response to the first-line therapy, and the presence of hormone receptors are important prognostic factors for survival and also predictive factors for subsequent chemotherapy. Additional studies should be focused to find effective treatment regimens for those patients with primary resistance to early lines of chemotherapy regimens.

Clinical Practice Points

- Cytotoxic chemotherapies for patients with MBC have shown improved survival and QoL.
- Around 5% to 17% of patients will develop primary resistance to first-line cytotoxic chemotherapy, and the proportion of chemotherapy resistance increased by two- to threefold in the subsequent line of therapy, regardless of hormone receptor positivity.
- Patients who had no response to previous therapy showed a strong tendency for failure with subsequent treatment regimens.
- The efficacy of previous treatment significantly affected the outcomes of subsequent treatment.
- The PFS of first-line therapy, the response to the first-line therapy, and the presence of hormone receptors were important prognostic factors for survival and also were predictive factors for subsequent chemotherapy.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental table accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clbc.2014.09.001.

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Supplemental Table 1 Chemotherapeutic Regimens in Each Line of Therapy

Regimen	Number of Patients (%)
First-line therapy (n = 240)	
Anthracycline based	44 (18.3)
AC	7
FAC	33
FAC + bevacizumab	4
Taxane based (D or P)	168 (70)
D	15
D + capecitabine	25
D + bevacizumab	1
P	72
P + cisplatin	5
P + gemcitabine	29
D + doxorubicin	18
Ixabepilone + capecitabine	3
Capecitabine based	28 (11.7)
Capecitabine + irinotecan	8
Capecitabine + bevacizumab	3
Capecitabine	14
S-1 + oxaliplatin	3
Second-line therapy (n = 209)	
Anthracycline based	46 (22)
AC	3
FAC	43
Taxane based (D or P)	47 (22.5)
D	19
P	21
P + cisplatin	1
Ixabepilone + capecitabine	5
RPR109881A	1
Capecitabine based	85 (40.7)
Capecitabine + irinotecan	28
Capecitabine	50
S-1 + oxaliplatin	7
G and/or V	31 (14.8)
G	5
G + cisplatin	7
G + V	10
V	9
Third-line therapy (n = 166)	
Anthracycline based	9 (5.4)
AC	1
FAC	8
Taxane based	6 (3.6)
D	3
P	2
P + cisplatin	1
Capecitabine based	56 (33.7)
Capecitabine + irinotecan	14
Capecitabine	39
S-1 + oxaliplatin	3
G and/or V	90 (54.2)
G	15
G + cisplatin	41
G + V	13
V	21
Other	5 (3.0)
Mitomycin C	4
Sunitinib	1

Supplemental Table 1 Continued

Abbreviations: AC = doxorubicin plus cyclophosphamide; D = docetaxel; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; G = gemcitabine; P = paclitaxel; V = vinorelbine.